Remarks

The Office Action mailed December 18, 2006 has been received and reviewed. Claim 18 having been amended, claims 22 and 27 having been canceled (claims 1-17 and 21 having been previously canceled), without prejudice, the pending claims are claims 18-20, 23-26, and 28-30. Reconsideration and withdrawal of the rejections are respectfully requested.

The 35 U.S.C. §103 Rejection

The Examiner rejected claims 18-30 under 35 U.S.C. §103(a) as being unpatentable over Hajduk et al.(*J. Am Chem Soc.*, 1997; 119:12257-12261) and in view of Keifer (*Drugs of the Future*, 1998; *23*(3):301-317). It is noted that claim 21 was previously cancelled. This rejection is rendered moot in view of amendment of claim 18; insofar as this rejection applies to the presently pending claims, it is respectfully traversed.

Applicants have developed a method that involves the use of a relaxation-editing binding assay based on NMR spectroscopy that eliminates the need to develop a high-throughput functional assay, and also allows the method to be used on molecular targets lacking a known function.

One important element that contributes to the success of Applicants' method is selection of a suitable library of compounds, which is neither taught nor suggested by the cited documents. Thus, claim 1 recites selecting a library comprising test compounds, wherein each test compound has a solubility in deuterated water of at least about 1mM at room temperature, and has a molecular weight of no greater than about 350 grams/mole.

Another important element that contributes to the success of Applicants' method is using relatively low concentrations of target molecule and near equimolar ratios of ligand to target. Thus, claim 1 recites wherein the concentration of target molecule and each test compound in each sample reservoir is no greater than about 100 μM; and wherein the ratio of target molecule to each test compound in each sample reservoir is about 1:1.

As stated in Applicants' specification at page 9, line 16, through page 11, line 3, for example:

> Important elements that contribute to the success of the methods of the invention preferably include developing a suitable small library of compounds to screen, carrying out the binding assay at low concentrations of target and near equimolar ratios of ligand to target (for relaxation-editing), . . . and the capacity for rapid throughput of data collection. For example, for relaxation-editing NMR techniques, the concentration of target molecule is preferably no greater than about 1.0×10^{-4} M. . . .
>
> The selection of compounds in a small library (preferably, at least about 75 compounds, more preferably, at least about 300 compounds, and most preferably, at least about 2000 compounds) is important in that its diversity should mimic the diversity of larger compound collections. Preferably, each component possesses many of the desirable qualities of a lead chemical template. These include water solubility, low molecular weight (preferably, no greater than about 350 grams/mole, more preferably, no greater than about 325 grams/mole, and most preferably, less than about 325 grams/mole), and amenability to synthetic chemistry elaboration. Templates possessing these qualities, as compared to a template selected randomly, are preferably considered to be predisposed to being lead-like and having an increased likelihood of ultimately leading to a drug.
>
> Good structural diversity in a library increases the likelihood that one or more compounds will possess structural characteristics important for binding to a given molecular target. Predisposing the compounds to be water soluble, to have low molecular weight (preferably, no greater than about 350 grams/mole, more preferably, no greater than about 325 grams/mole, and most preferably, less than about 325 grams/mole), and to be amenable to synthetic elaboration increases the likelihood that a compound found to be a ligand will lead to a related compound or compounds suitable as a lead chemical template for use, for example, in a process of identifying an effective therapuetic and/or prophylactic agent. Additionally, the requirement for good water solubility (preferably, at least about 1.0×10^{-3} M in deuterated water at room temperature) is important in that it increases the likelihood of success of other downstream drug-design projects, such as co-crystallization attempts, calorimetry studies, and enzyme kinetic analyses.
>
> Carrying out a relaxation-editing binding assay (preferably, a 1D ^{1}H NMR assay) at low concentrations of target (preferably, no greater than about 1.0×10^{-4} M, and more preferably, no greater than about 5.0×10^{-5} M) and near equimolar ratios of ligand to target creates the requirement that compounds testing positive for binding have affinities within a factor of about 3-4 of this same concentration (preferably, having a dissociation constant of no less than about 2.0×10^{-4} M). . . . This level of affinity is desired if the subsequent steps of focused screening and directed chemical elaboration are to be successful in elucidating a lead chemical template with very low affinity. . . . Carrying

out the initial screening at these low concentrations also avoids detection of unwanted compounds with much smaller dissociation constants in the 1.0×10^{-3} M range, which are less specific in their binding and therefore harder to turn into lead chemical templates given their weak affinity initially.

The combination of Hajduk et al. and Keifer does not teach or suggest each and every aspect of Applicants claimed invention. For example, this combination does not teach or suggest the characteristics of a library that are important in successfully implementing the claimed method. This combination does not teach or suggest the relative amounts and ratios of target molecule and ligand that are important in successfully implementing the claimed method.

Applicants have selected a library that includes specific test compounds ("wherein each test compound has a solubility in deuterated water of at least about 1mM at room temperature, and has a molecular weight of no greater than about 350 grams/mole") that can be used effectively at relatively low concentration ("wherein the concentration of target molecule and each compound in each sample is no greater than 100 μM") and at near equimolar ratios of target molecule and test compounds. Such combination of elements contributes to the identification of compounds with similar affinity and avoids detection of unwanted compounds that are less specific in their binding and harder to turn into lead chemical templates (see, e.g., Applicants' specification at page 10, line 19 through page 11, line, 3). From a practical perspective, the solubility requirement is also important to avoid clogging the flow-injection probe.

It is respectfully submitted that this combination of elements and the advantages they provide are not taught, suggested, or appreciated by either Hajduk et al. or Keifer or the combination thereof. Thus, withdrawal of the rejection is respectfully requested.

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Summary

It is respectfully submitted that the pending claims 18-20, 23-26, and 28-30 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to **Mail Stop AF**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 15th day of February, 2007, at 11:03 pm (Central Time).

By: Danielle Munoz
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